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Original Research Article

Evaluation of serum placental growth factor in predicting pregnancy outcomes in women with suspected pre-eclampsia

Fariba Kahnamouei-aghdam[1], Farhad Pourfarzi[2], Samaneh Ehsani[1]*

[1]Department of Obstetrics and Gynecology, [2]Department of Community Medicine, School of Medicine, Ardabil University of Medical Science, Ardabil, Iran

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***Correspondence:**
Dr. Samaneh Ehsani,
E-mail: samaneh.ehsani2016@gmail.com

ABSTRACT

Background: Amount of Placental Growth Factor (PLGF) in the blood at 9 to 11 weeks before the onset of clinical signs of pre-eclampsia is reduced. So, diagnostic tests based on the pathophysiology of disease such as PLGF as an ideal marker for early screening in the diagnosis and management of women with preeclampsia, may be useful. The aim of this study was to investigate PLGF in predicting pregnancy outcome in women with suspected pre-eclampsia.
Methods: A case - control study was conducted on 30 women with suspected pre-eclampsia and 101 healthy pregnant women which selected randomly among all pregnant women referred to clinic. Both groups were followed until pregnancy termination and in terms of pregnancy outcomes (Gestational age, Type of delivery and birth weight). Two groups were matched in terms of age, weight, education, substance abuse and socio-economic status. Placental growth factor assay was done by ELISA kit. Data collected by a checklist and analyzed by statistical methods in SPSS.19.
Results: The mean PLGF level was lower for women who experienced preeclampsia compared with healthy women (71.5 pg/ml vs 272.1 pg/ml, p=0.001). Also, PLGF concentrations was very low in women with preeclampsia who had a preterm birth prematurity.
Conclusions: Study findings identified PlGF as an ideal, simple and non-invasive marker for primary screening at prenatal care for women at risk of pre-eclampsia.

Keywords: Placental growth factor, Preeclampsia, Pregnancy outcome

INTRODUCTION

Preeclampsia (PE) is a major cause of maternal mortality in worldwide which affecting 2 to 8% of all deliveries. The prevalence of preeclampsia in pregnancy is 5-8% and its incidence is common in nulliparous pregnancy.[1,2]

The exact theory and mechanism of pre-eclampsia is still unknown. Pre-eclampsia is one of the common disorders during pregnancy which had been associated with increasing blood pressure in the second half of pregnancy and proteinuria. It considered by the World Health Organization as one of the women health issues.[3]

Usually, PE occur in the second half of pregnancy and is known as a systematic disorder which deal to HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count) and the causes of most cases remains unknown.[4,5]

Circulating levels of PLGF have been reported to be reduced in women with preeclampsia. Based on these findings, it was hypothesized that circulating

PLGF may be a predictor of preeclampsia. Several studies with conflicting results have recently been published on the predictive value of mid gestational

PLGF plasma concentrations in early identification of pregnant women at risk of developing preeclampsia.[6]

Verlohren et al. reported that the sFlt-1/PLGF ratio is important to identify women at risk for delivery and a reliable tool to discriminate between different types of pregnancy-related hypertensive disorders. In women with suspected preeclampsia at < 34 weeks, the circulating sFlt1/PLGF ratio predicts adverse outcomes which occur within two weeks.[7-9]

PLGF is an angiogenic growth factor related to vascular endothelial growth factor that is exclusively produced by the trophoblast. In normal pregnancy, levels of PLGF increase throughout gestation, peaking at approximately 26–30 weeks. Decreasing levels of PLGF have consistently been found throughout gestation and associated with pre-eclampsia. PLGF levels have also been reported to be low in the first trimester at women who subsequently developed preeclampsia compared to women with normal pregnancy, despite the suggested role of PLGF as a first-trimester predictor of pre-eclampsia, a recent study using urinary PLGF levels in the first trimester failed to confirm this relationship.[10-12]

Placental growth factor (PLGF) is a member of the vascular endothelial growth factor family and is implicated in angiogenesis and trophoblastic invasion of the maternal spiral arteries. Maternal serum levels of PLGF at 11–13 weeks' gestation is decreased in pregnancies with fetal aneuploidy and those with impaired placentation resulting in pre-eclampsia (PE) and delivery of small-for-gestational-age (SGA) neonates. Serum levels of PLGF are also reduced in the second and third trimesters of pregnancies that develop PE or deliver SGA neonates.[7,13-23]

While the pathophysiology of preeclampsia is not yet fully understood, there is growing evidence associating angiogenic proteins in screening, diagnosing and predicting the clinical course of the condition.[8,10,24,25] Placental growth factor (PLGF) is a proangiogenic marker that circulates at high concentrations in normal pregnancies. In pregnancies complicated by preeclampsia, circulating levels of unbound PLGF are decreased.[2,3]

METHODS

A case-control study was conducted on 30 women with suspected preeclampsia and 101 healthy pregnant women in the gestational age 20 to 40 weeks which selected randomly of women who visited a specialized clinic. The patients who have read and signed the consent form, entered the study. The two groups were similar in their job, weight, education, drug misusage, social and economic status and gestational age. Pre-eclampsia was defined as BP ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest) and proteinuria is 300 mg/24 hours; or ≥1+ (on 2 random urine samples, collected at least 4 hours apart); or protein: creatinine ratio is ≥0.3 mg/dL. The inclusion criteria were to have the age between 15 and 35, Singleton pregnancy, no history of gestational diabetes and lack of kidney issues during the current pregnancy. All women in two groups were followed until the end of the pregnancy and at the end, in terms of pregnancy (gestational age, type of delivery and neonate's birth weights) were studied. Of the women, an interview was taken by a checklist and pre-eclampsia was followed by clinical tests and examination. 2 cc of blood was taken of the women in two groups and after extracting the serum, the samples were restored in temperature of minus 20 ^{0}C and then, end of sampling, Placental growth factor assay was done by ELISA kit Cusabio. China CSB-EO470. Collected data were analyzed by statistical methods in SPSS.16.

RESULTS

The mean gestational age in the preeclampsia women was 33.7 and in healthy women was 33.3 weeks (P= 0.035). There was significant difference between two groups in term of characterized such as age, HR, Systolic and Diastolic Blood Pressure (Table 1).

Table 1: Characteristics of study population in two groups.

Characteristics of study population	Healthy women	Preeclamptic women	p-value
Gestational age	33.4±4.4	33.7±3.75	0.035
Age	28.4±4.4	30±4.4	0.03
Height	1.62±0.5	1.61±0.7	0.25
Weight	70.5±12.8	72±10.3	0.26
Weight in pregnancy time	78.3±10.3	81.5±13	0.06
BT	36.9±0.24	36.8±0.3	0.4
HR	72.8±18.4	79±5.7	0.03
BP Systolic (mmHg)	106±7.8	122±19.7	0.001
BP Diastolic (mmHg)	68.1±5.9	75±13.6	0.001

In the preeclampsia women, most of patients due to high blood pressure and in healthy women due to childbirth pain had come to the clinic.

There was significant difference between two groups in term of pregnancy outcomes such as mode of delivery, termination age of pregnancy, birth weight and hospitalization due to pregnancy side-effects (Table 2).

The PLGF serum level in the preeclamptic women with 68.1 pg/mL was significantly lower than the healthy women with 268.9 pg/mL and in healthy women, 82.2% and in preeclamptic women 73.3% had PLGF (between 12-5th centile) (Table 3).

Table 2: Pregnancy outcomes.

Pregnancy outcome	Healthy women N=101	Preeclamptic women N=30	p-value
Mode of delivery			
Vaginal	52.5	96.7	0.001
Cesarean Section	47.5	3.3	
Termination age of pregnancy			
Pre-mature preterm birth	0	13.3	0.001
Post-mature preterm	2.7	60	
Term birth	76.3	26.7	
Birth weight (g)			
<1500	9.9	26.7	0.001
1500-2500	0	13.3	
>2500	90.1	60	
HELLP Syndrome (%)			
Yes	0	3.9	0.12
No	100	96.1	
Hospitalizaton because of neonatal problems (side-effects) (%)	21.8	66.7	0.001

Table 3: PLGF levels in two groups.

PLGF values (pg/mL)	healthy pregnant women		women with suspected pre-eclampsia		p-value
	n	%	n	%	
<12 pg/ml (very low)	-	-	2	6.7	0.001
12 pg/ml-5th centile (low)	18	17.8	22	73.3	
>5th centile (Normal)	83	82.2	6	20	
Total PLGF	268.9±23.2		68.12±11.4		0.001

In the pre-eclampsia women who had premature preterm, 50% had PLGF low than 12 pg/mL and in mothers with cesarean delivery, 72.4% of and in mothers had babies more than 2500 gr, 75% and in mothers had pregnancy side-effects, 50% had PLGF in ranged 12 to 5th centile. (Table 4).

DISCUSSION

In the study of Maynard and et al that was done to analyze the serum level of PLGF in the second trimester of pregnancy in order to predict pre-eclampsia, 61 pregnant mothers with the gestational age of 15-18 weeks were followed and studied that 11.4% were diagnosed with pre-eclampsia which PLGF level in these patients were significantly low which in line with our study results. The difference in the incidence rate of pre-eclampsia in two studies can be related to selected study population.[26] The results of this study showed that 96.8% of the mothers in the preeclamptic women and 53% of the control group had cesarean that this rate was statistically significant between two groups (P=0.001).

Table 4: PLGF values by pregnancy outcome in preeclamptic women.

PLGF values Pregnancy outcome	<12 pg/ml (very low) n(%)	12 pg/ml-5th centile (low) n(%)	>5th centile (normal) n(%)	p-value
Mode of delivery				
Vaginal	-	1(100)	-	0.88
Cesarean Section	2(6.7)	21(72.4)	6(20.8)	
Termination age of pregnancy				
Chronic Pre-mature preterm	2(50)	2(50)	-	0.001
Post-mature preterm	-	8(100)	-	
Term	-	12(66.7)	6(33.3)	
Birth weight (g)				
<1500	2(25)	6(75)	-	0.04
1500-2500	-	4(100)	-	
>2500	-	12(66.7)	6(33.3)	
Pregnancy Side effects				
Yes	2(50)	2(50)	-	0.001
No	-	20(76.9)	6(23.1)	

In Gullai and et al study the results revealed that all of the blood pressure types, PLGF was notably lower than control group and lower PLGF test was the predictor of preterm birth.[27] In the preeclamptic women, 7.2% of the mothers had babies under the weight of 1500 gr, 9.28% of the babies were 1500-2500 gr and 88.35% of the babies were over 2500 gr which on the aspect of birthweight there was a significant difference between two groups (P=0.02).

In 21.4% of the preeclamptic women and 23.3% of the control group, babies were hospitalized after birth which was no significant difference between two groups. The analysis of PLGF serum level in the studied patients showed that in mothers diagnosed with pre-eclampsia the average PLGF serum level is 71.51 that varies from 11.31 to 226.71. In healthy mothers the average of PLGF was 272.11 which is variant from 16.92 to 1552.7. There was a significant difference in serum level of pregnant women who are diagnosed to pre-eclampsia and the ones that are not (P=0.000). In Rana and et al (2012) study, PLGF level and sFLt 1 in pre-eclampsia patients was abnormal compared to the control group but in comparison of sever and mild pre-eclampsia patients only the level of PLGF had significant difference.[21] The rate of PLGF in blood is reduced before the onset of symptoms in 9 to 11 weeks and this is in a way that this level notably decreases 5

weeks before the increment of blood pressure and proteinuria.[13]

The analysis of normal and abnormal level of PLGF reveal that in mother diagnosed with pre-eclampsia, 70.4% and in mothers without pre-eclampsia 24% have PLGF of 12-100 and none of them had PLGF under 12. The results of this study have revealed that all of the mothers diagnosed with pre-eclampsia who had premature preterm birth, had abnormal PLGF. In the mothers diagnosed with pre-eclampsia who had term pregnancy, 100% had PLGF of between 12 and 5th centile (abnormal). In the study of Gullai and et the results showed that in all types of blood pressure types in pregnancy, PLGF was notably lower than control group and positive PLGF test predicts preterm childbirth in women diagnose with pre-eclampsia in Vrlohream's study it was revealed that the time between diagnosis to pregnancy completion among pre-eclamptic women with high sFLt/PLGF ratio had notably decreased.[7,27] In the study of Chappell and et al, it was determined that PLGF is valuable in managing of pregnant mothers suspicious to pre-eclampsia especially preterm. Low levels of PLGF (under 100 pg/ml) has high sensitivity and negative predictive value in determining the pregnant women who need pregnancy completion in 14 days due to pre-eclampsia which was similar to our study results.[23]

The analysis of serum level of PLGF in preeclamptic mothers with cesarean childbirth showed that 7.4% had PLGF of 12 and 70.4% had PLGF of 12-5th centile (abnormal) and 22.2% had PLGF of over 5th centile (normal).

The relation between serum level of PLGF and birthweight of babies in pregnant mothers diagnosed with pre-eclampsia showed that all of mothers who have babies under 1500 gr, have abnormal PLGF (28.6% under 12 and 71.4% PLGF between 12 and 5th centile). In preeclamptic mothers who had babies from 1500 to 2500 grams, all have PLGF between 12 and 5th centile (abnormal) and in preeclamptic mothers who had babies over 2500 grams, 64.7% have PLGF of 12 to 5th centile (abnormal) and 35.3% had normal PLGF.

Some studies have demonstrated that PLGF concentrations begin to decrease from 9-11weeks before the onset of preeclampsia, with greatest reductions during the 5 weeks before the onset of hypertension or proteinuria. Also, Aljebory and et al in a study showed that utility of PLGF as an accurate and specific marker identifying the underlying cause of disease, placental dysfunction is supported by evidence which was in line with our study results.[28]

CONCLUSION

Study findings identified PLGF as an ideal, simple and non-invasive marker for primary screening at prenatal care for women at risk of pre-eclampsia. Also, in conclusion, we found that when women were evaluated for preeclampsia, the PLGF concentration exactly could predict adverse outcomes particularly among women have <34 WG, and is a good test or marker for management of women with preeclampsia. So, doing more studies in this regard in more sample is essential in future.

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